A population-based survival analysis describing the association of body mass index on time to revision for total hip and knee replacements: Results from the UK General Practice Research Database

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Complete List of Authors:	Culliford, David; University of Southampton, Faculty of Medicine Maskell, Joe; University of Southampton, Public Health Sciences and Medical Statistics Judge, Andrew; University of Oxford, NIHR Musculoskeletal Biomedical Research Unit; University of Southampton, MRC Lifecourse Epidemiology Unit Arden, Nigel; University of Oxford, NIHR Musculoskeletal Biomedical Research Unit; University of Southampton, MRC Lifecourse Epidemiology Unit
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A POPULATION-BASED SURVIVAL ANALYSIS DESCRIBING THE ASSOCIATION OF BODY MASS INDEX ON TIME TO REVISION FOR TOTAL HIP AND KNEE REPLACEMENTS: RESULTS FROM THE UK GENERAL PRACTICE RESEARCH DATABASE.

STUDY DESIGN: Population-based study.

AUTHORS' NAMES AND AFFILIATIONS

David Culliford (Senior Medical Statistician)[1]

Joe Maskell (Data Manager)[2]

Andy Judge (Senior Medical Statistician)[3,4]

Nigel K Arden (Professor of Rheumatic Diseases and Director)[3,4]

and the COAST Study group

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

ABSTRACT

Objectives Against a backdrop of rising levels of obesity, we describe and estimate associations of body mass index (BMI), age and gender with time to revision for subjects undergoing primary total hip (THR) or knee (TKR) replacement in the UK.

Design Population-based cohort study

Setting Routinely collected primary care data from a representative sample of general practices, including linked data on all secondary care events.

Participants Population-based cohort study of **63,162** THR and **54,276** TKR patients in the UK General Practice Research Database between 1988 and 2011.

Primary and secondary outcomes Risk of THR and TKR revision associated with BMI, age and gender, after adjusting for the competing risk of death.

Results The five-year cumulative incidence rate for THR was 2.2% for men and 1.8% for women (TKR: 2.3% for men, 1.6% for women). The estimated adjusted subhazard ratios for THR patients undergoing subsequent hip revision surgery, with a competing risk of death, were 1.020 (95% CI: 1.009, 1.032) per additional unit (kg/m^2) of BMI, 1.23 (95% CI: 1.10, 1.38) for men compared with women and 0.970 (95% CI: 0.967, 0.973) per additional year of age. For TKR patients, the equivalent estimates were 1.015 (95% CI: 1.002, 1.028) for BMI; 1.51 (95% CI: 1.32, 1.73) for gender, and 0.957 (95% CI: 0.951, 0.962) for age. Morbidly obese THR patients had a 65.5% increase (95% CI: 15.4%, 137.3%, p=0.006) in the subhazard of revision versus the normal BMI group (18.5 to 25). The effect for TKR was smaller (a 43.9% increase) and weaker (95% CI: 2.6%, 103.9%, p=0.040).

Conclusions Body mass index is estimated to have a small but significant association with the risk of hip and knee revision, but absolute numbers are small. Further studies are needed in order to distinguish between effects for specific revision surgery indications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Published revision rates for hip and knee replacement already exist, based on UK-based registry data, but follow-up periods are still relatively short.

Some evidence exists that obesity is a risk factor for undergoing primary total hip and knee replacements, but there is little in the literature for the risks of raised BMI on revision surgery.

The recording of BMI prior to primary total hip or knee replacement is less than complete in most national joint registries.

WHAT THIS STUDY ADDS

Body mass index is estimated to have a small positive association with the risk of hip and knee revision, after allowing for the competing risk of death.

The elevated risk of revision of the hip in morbidly obese (> 40 kg/m^2) patients during the first year after primary replacement is not observed in the knee.

It would take 175 TKR patients (152 for THR) to reduce their baseline BMI from obese to normal in order to prevent one revision operation after 5 years.

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Article focus

▪ Total joint replacement of the hip (THR) or knee (TKR) is commonly used as an intervention for patients with end-stage osteoarthritis of the lower limb.

▪ Joint prostheses sometimes require revision surgery and it is important for surgeons, patients and policy makers to understand the risk factors for time to revision.

▪ Although many studies modelling the time to joint revision have taken over the past 30 years, few such studies have been large-scale, population-based, competing risks analyses.

Key messages

▪ These data from the GPRD shows a small but significant association between body mass index and the time to revision for both hip and knee replacement.

▪ The risk of hip replacement revision for morbidly obese patients was two-thirds higher than for those with normal body mass index.

▪ The use of competing risks methods produced similar estimates of revision risk to those obtained using relative risks regression methods.

Strengths and potential limitations of the study

▪ The large sample size of the GPRD (over 5% of the UK genral practice population) enables population-level inferences to be made

▪ The statistical methods explicitly account for the competing risk of death which has a much higher event rate than the event of interest (THR or TKR) in this patient group.

▪ GPRD data does not have directly linked information detailing the reasons for being referred for surgery, so we were unable to establish an exact indication.

INTRODUCTION

Total joint replacement of the hip and knee are well established as interventions for those suffering with end-stage osteoarthritis (OA) of the lower limb, with OA being the most frequent indication for total hip or knee replacement in the UK(1) (over 90% for hips and over 95% for knees). Yet hip and knee prostheses do not necessarily continue to function effectively for the lifetime of the patient(1, 2). Many traditional metal-on-polyethylene implants are likely to require revision surgery due to wear after 20 years of use due to wear characteristics and peri-prosthetic loosening. As a consequence, elective THR and TKR procedures have until relatively recently been indicated mainly in older patients, but even prostheses which make use of the latest technological developments (*e.g.* unicondylar knee prostheses) are not yet routinely recommended for use in younger patients.

A further dimension is added by the increasing prevalence of obesity in western populations, with clinicians in some cases considering patients too obese to undergo surgery(3, 4), partly due to the perceived increase in risk of both peri- and post-operative complications. There have also been examples of obese and/or morbidly obese patients experiencing restricted access to hip replacement surgery in some parts of the UK(5-7) where local healthcare planners have had similar concerns.

Revision procedures involve a surgical intervention to correct a prosthesis which is not functioning properly. Such operations are more costly than the original replacement procedure(8, 9). Population-based estimates of the time from primary surgery to a revision procedure are of importance to orthopaedic surgeons, rheumatologists, healthcare providers, policymakers and patients. Registry data, both in the U.K.(1) and internationally(10, 11), have been used extensively to estimate time to revision(12). Such data has been used previously to model prosthesis survival time in order to assess which specific demographic, clinical and prosthesis-specific factors are associated with time to failure(13, 14).

Over the 12 months to April 2011, there were over 178,000 total hip and knee replacement operations recorded in the National Joint Registry for England and Wales(1). However, although the registry contains complete data on many variables, including age and gender, body mass index is recorded in approximately 61% of subjects undergoing hip replacement (62% for knee).

The primary aim of this study was to use data from the General Practice Research Database to produce population-based estimates for the association of body mass index, age and gender with the time to revision surgery in the long term following a THR or TKR.

METHOD

Participants

We used data from the General Practice Research Database (GPRD). The GPRD comprises the entire computerized medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from over 600 contributing practices chosen to be representative of the wider UK population(15). GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD has recently become part of the new Clinical Practice Research Datalink (CPRD) which is administered by the Medicines and Healthcare products Regulatory Agency (MHRA).

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. The GPRD comprises entire general practice populations rather than probability-based samples of patients.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1991 until August 2011. We then identified any secondary (revision) hip or knee operations for these patients which occurred subsequent to the primary operation. Deaths recorded within the GPRD were also identified. The date of the first incidence of a subject's hip or knee replacement was used as the start time. The event of interest in all time-to-event models was the first recorded revision operation. Censoring events were the end of study date (11th August 2011) or the transfer of a patient out of the GPRD for any reason other than death. Death from any cause was treated as a competing risk in the primary analysis. Patients were included in the analysis if aged 18 years or over at the time of the replacement operation. Participant demographics including age, gender, body mass index (BMI), smoking and drinking status were collated, in addition to information on comorbid conditions.

Analysis

We used the competing risks regression methods of Fine and Gray(16) to estimate the effects of a subject's body mass index (BMI), age and gender on the time to revision of a prosthesis implanted during a THR or TKR operation. The substantive event of interest was the first incidence of revision surgery, with all-cause mortality separately identified as a competing risk. The rationale for using competing risks regression is that methods which treat death as just another censoring event may overestimate risk for an event of interest, especially in an older population(17). We adjusted for a range of important covariates and potential confounders: smoking status, alcohol consumption and the number of comorbid conditions (which include diabetes, hypertension, stroke, cardiovascular disease and anaemia). All covariates were treated as fixed at baseline. Analyses for hips and knees were performed separately, with prosthesis survival at the end of follow-up being of primary interest. Proportionality of hazards assumptions was assessed by examining complementary log-log plots of the cumulative incidence. As a sensitivity analysis we modelled the same data using standard methods which do not cater for competing risks (*i.e.* Cox regression analysis with death as a censoring event). We also calculated stand-alone estimates for the cumulative incidence of revision surgery at 1, 5, 10 and 15 years, and plotted estimates of the age-, gender- and BMI-specific cumulative incidence curves for the whole cohort.

All tests of significance were at the 5% level and two-sided. Interval estimates were based on 95% confidence intervals. The main statistical analysis was carried out using R (R Core Team, 2012. R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.2 (SAS Institute Inc., Cary, NC) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX).

RESULTS

Participant demographics

Over the study period the database contained 63,162 patients undergoing total hip replacement and 54,276 patients undergoing total knee replacement. The average age at replacement was similar in both the THR and the TKR groups but the proportion of women was greater for both THR and TKR (table 1). For those with a recorded pre-operative BMI, the proportion of obese subjects (BMI >=30 kg/m^2) was 26.2% for THR and 39.8% for TKR and the proportion of morbidly obese subjects (which we define as having a BMI >=40 kg/m^2) was 1.6% for THR and 3.6% for TKR. Table 1 describes the baseline characteristics of the cohort, including summary statistics and missing data percentages for all explanatory variables where complete data was not observed.

Survival analysis

The estimated cumulative incidence of revision at five years was 2.0% (95% CI: 1.8, 2.1) for THR and 1.9% (95% CI: 1.8, 2.1) for TKR. For women, cumulative incidence at five years was 1.8% (95% CI: 1.7, 2.0) for THR and 1.6% (95% CI: 1.5, 1.8) for TKR, and for men 2.2% (95% CI: 2.0, 2.4) and 2.3% (95% CI: 2.1, 2.6) respectively. Table 2 provides gender-specific estimates of cumulative incidence with point-wise confidence intervals for a range of times (1, 3, 5, 10 and 15 years after THR/TKR). Figures 1 and 2 provide a further breakdown of the cumulative incidence of revision for the whole THR and TKR cohorts respectively, with separate incidence curves for categorised BMI (figure 1) and categorised age (figure 2). Gray's test was used to examine whether there were overall differences in the cumulative incidence of revision by gender, categorised age (<55, 55-64, 65-74, 75-84, >85 years) and categorised BMI (<18.5, 18.5-24.9, 25-29.9, 30-39.9, >40 kg/m^2). All three variables showed statistically significant differences in cumulative incidence for both hip (Gray's test statistic: gender, age, BMI, p<0.001 for all) and knee (Gray's test statistic: gender, age, BMI, p<0.001 for all).

In a single predictor (univariable) survival model allowing for the competing risk of death, we found that the subhazard of revision was significantly greater for men compared to women for both THR (subhazard ratio [SHR]: 1.35, 95% CI: 1.23, 1.48, p<0.001) and TKR

2.0% (SHR: 1.54, 95% CI: 1.37, 1.72, p<0.001). Age at total joint replacement was also a significant predictor of revision for both hip and knee, with THR subjects estimated to have a 3% reduction in the subhazard of revision (SHR: 0.970, 95% CI: 0.967, 0.973, p<0.001) for each extra year of age, with TKR subjects showing a 4.3% reduction (SHR: 0.957, 95% CI: 0.952, 0.961, p<0.001). The univariable model for body mass index estimated that THR subjects had a 3.0% increase in the subhazard of revision (SHR: 1.030, 95% CI: 1.020, 1.041, p<0.001) for each extra unit (kg/m^2) of BMI, with TKR subjects showing a 2.6% increase per unit (SHR: 1.026, 95% CI: 1.013, 1.038, p<0.001).

The effects for all three variables (gender, age and BMI) were then estimated in multivariable competing risks regression models after adjusting for smoking status, drinking status and the number of comorbid conditions. For age, the estimates for the subhazard of revision were almost exactly the same as those from the univariable model for both hip and knee, but for gender (SHR: 1.23 for hip; 1.51 for knee) and BMI (SHR: 1.020 for hip; 1.015 for knee) the estimates were smaller. Nevertheless, all three variables remained statistically significant for both hip and knee in the presence of adjustment. Testing for two-way interactions between age, gender and BMI did not produce any significant effects. All subhazard estimates (with 95% confidence intervals and p-values) from the univariable and multivariable models are given in table 3.

To further explore the effect estimates for BMI we ran the same adjusted age-gender-BMI model described above, but used categorical BMI instead of continuous. For morbidly obese TKR subjects (BMI 40+) there was a 43.9% increase (95% CI: 2.6%, 103.9%, p=0.040) in the subhazard of revision compared to those with a normal BMI (18.5 to 25), but the effect for THR was larger (a 65.5% increase) and stronger (95% CI: 15.4%, 137.3%, p=0.006). The effect sizes were similar to those obtained when using the adjusted subhazard ratio estimate of continuous BMI for a subject with a BMI of 45 relative to one with a BMI of 22 (increase of 57.7% for THR; 40.8% for TKR). For obese patients in the range 30 to 40 kg/m^2 versus those with a normal BMI, the estimated subhazard ratio for revision was weakly significant for THR (15.7% increase, 95% CI: 0.2%, 33.7%, p=0.048) but not for TKR (17.9% increase, 95% CI: -1.9%, 41.6%, p=0.079).

As a sensitivity analysis, we also performed standard Cox regressions with revision surgery as the event of interest and where no distinction was made between death and other censoring events. Univariable models for age, gender and BMI gave very similar results to the competing risks analysis, as did the multivariable models which adjusted for the same factors as in the competing risks regression. Results from the Cox regression models are given in table 4.

Finally, we assessed whether the higher incidence of hip revision surgery during the first year following THR (see figures 1a and 2a) might compromise the proportionality assumption and therefore suggest the inclusion of time-dependent effects. Separate univariable piecewise competing risks models for hip revision were fitted for gender, age (<= 65 years vs. > 65) and BMI (> 40 vs. <= 40). A single changepoint at one year was used to simultaneously estimate two subhazard ratios for revision (before and after one year following THR). The only model which provided some evidence for a different subhazard ratio during the first year was with BMI (> 40 vs. <= 40) as the predictor (SHR: 2.619, 95% CI: 1.502, 4.560, p=0.001), but this was not matched with a statistically significant estimate for revision after the first year (SHR: 0.575, 95% CI: 0,238, 1.170, p=0.130).

DISCUSSION

This study presents population-based estimates for the risk of revision following total joint replacement of the hip and knee using methods from survival analysis. Cumulative incidence rates of revision were higher for men than for women and higher for hips than knees. Age, gender and body mass index were estimated to be significant predictors of time to revision in an adjusted model allowing for the competing risk of death. Severely obese patients undergoing total hip replacement were observed to have a higher risk of revision surgery during the first year following replacement, but the same effect was not observed for knee replacement.

The literature on obesity as a risk factor for hip and knee arthroplasty concentrates mainly on the risk for primary replacement rather than for revision procedures, and most use rate differences to estimate relative risk, rather than using time-to-event methods. Many published studies are small and do not have sufficient power to detect rare outcomes. Often these studies are locally based and the generalisability to population level is questionable. Mostly results are presented for categorised BMI, which is often dichotomised at 30 kg/m^2, and where results for the morbidly obese are reported, the sample size is small.

One of the largest studies examining primary replacement followed up a cohort of over 490,000 middle-aged women over an average of 2.9 years and found increased incidence of hip and knee replacement in obese subjects(18). Of the studies which consider the effect of obesity on outcomes after primary joint replacement, several focus mainly on events such as complications arising from surgery(19) or subsequent admission to an intensive care unit(20), rather than the time to revision surgery. Among studies of other non-revision outcomes, Andrew *et al*(21) looked at the change in Oxford Hip Score five years after THR and found no difference between non-obese, obese and morbidly obese patients, but in a smaller study(22) using Harris Hip Score (HHS) with the same length of follow-up, an increase in BMI was associated with a small but significant reduction in HHS.

An editorial on obesity and joint replacement in 2006(23) suggested that it is those with a BMI of greater than 40 units (rather than 30) who are at risk of worse outcomes, yet several subsequent studies have used a BMI cut-point of 30 kg/m^2. A recent Australian study of 2026 THR and 535 TKR patients found no difference in mid-term survival rates between the obese (BMI > 30 kg/m^2) and non-obese(24). Another study from Switzerland used Cox regression to estimate the risk of revision in 2495 THRs using the same cut-point for BMI, estimating a non-significant adjusted hazard ratio for revision of 2.2 (95% CI: 0.9 to 5.3) for obese versus non-obese patients(19). However, a recent Canadian study of 3290 THRs did categorise BMI to include a morbidly obese group (BMI > 40 kg/m^2) and although the authors found no difference in time to revision between BMI categories in an unadjusted analysis, there was a marginally significant difference for septic revisions(25).

Our results suggest that there may be a 1.5% to 2% rise in the risk of knee and hip revision respectively for each extra unit of BMI. However, there is some variation in risk across the entire range of observed BMI values. For hips, there appears to be very little difference in BMI-related risk between the normal weight and overweight categories. However, figure 1a shows that for hips there may be a revision rate of approximately 6% for the morbidly obese after 10 years, against a 3% rate for the normal and overweight. For knees, figure 1b shows a more even distribution across the BMI categories up to about 7 years after TKR, but with higher risk for the morbidly obese between 7 and 10 years after TKR.

Although recommendations(26, 27) to consider the use of the cumulative incidence function for analysing prosthesis survival are gaining acceptance(28), the use of competing risks regression to model associated risk factors is still not widely observed. The justification for using competing risks methods in our primary analysis is that hip and knee prostheses are mainly implanted in older patients for whom mortality is a substantial competing risk which may be several times greater than the risk of revision. What is perhaps surprising is that our results show little difference between the hazard and subhazard ratio estimates from the Cox and the competing risks regression models respectively, although the former has a cause-specific interpretation with no distinction between death and censoring whereas the latter directly models the cumulative incidence of revision.

Strengths and potential limitations of the study

The strengths of the study data more than make up for its limitations. GPRD data has individual date-stamped records of patient event data in primary and secondary care settings, including data on many potential confounders, including comorbidities, BMI, smoking and drinking. The GPRD practice network covers all of the United Kingdom, and approximately 5% of all practices are covered by the GPRD. The high degree of generalisability afforded by this very large sample enables population-level inferences to be made. Follow-up is long, with several hundred prostheses in the dataset having over 20 years of follow-up without being revised. The choice of the statistical methods used to allow for the competing risk of death adds a further degree of robustness to the study. The regression estimates of the hazard ratio for body mass index as a factor associated with revision benefit from a precision which is not usually achievable outside of national registers, especially for the group of morbidly obese patients within which event rates in the literature are low.

There are several limitations to this work. The revision rate estimates hip and knee at 5 years are close to, but slightly less than those reported by the National Joint Registry, but the GPRD data used in this study includes prostheses implanted from the late 1980s. Also our data does not have directly linked information on the indication for surgery, which would have been enabled a sub-analysis by reason for revision.

CONCLUSION

This study has presented estimates of rates and risk factors for revision surgery on hip and knee prostheses using one of the largest available population-based sets of joint replacement data outside of national arthroplasty registries. Our estimates suggest that body mass index is positively associated with the risk of hip and knee revision, but studies of register data linked with sources of demographic and clinical data are needed in order to distinguish between effects for specific indications for revision surgery.

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Author affiliations

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

Collaborators The following people are members of the COAST Study group: Cyrus Cooper, Mark Mullee, James Raftery, Andrew Carr, Andrew Price, Kassim Javaid, David Beard, Douglas Altman, Nicholas Clarke, Jeremy Latham, Sion Glyn-Jones and David Barrett.

Contributors DJC, JM, AJ and NKA were involved in:
(1) substantial contributions to conception and design, analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

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Data sharing statement No additional data are available.

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Table 1 Clinical and Demographic characteristics – all subjects undergoing Total Hip or Knee Replacement

	Total Hip Replacement (N=63,162)		**Total Knee Replacement** (N=54,276)	
	Female (N=39,292)	Male (N=23,870)	Female (N=31,682)	Male (N=22,594)
Age (mean, SD)	70.5 (11.1)	67.7 (11.0)	70.7 (9.6)	69.4 (9.4)
Gender (%)	62.2	37.8	58.3	41.6
BMI (mean, SD)	27.2 (5.1)	27.7 (4.3)	29.6(5.6)	28.8(4.4)
Missing BMI (%)	19.1	19.3	13.8	14.0
Revisions (N, %)	1000 (2.55)	811 (3.40)	572 (1.8)	614 (2.7)
Deaths pre-revision (N, %)	6615 (16.8)	4201 (17.6)	4110(13.0)	3349 (14.8)
Number of comorbid conditions (%):				
0	42.8%	48.1%	37.5%	43.7%
1	34.2%	31.0%	37.4%	35.8%
2+	23.0%	20.9%	25.2%	20.6%

Table 2 Cumulative incidence rates for revision surgery at selected times following THR and TKR

	Hip				Knee			
	Female		Male		Female		Male	
Years since total joint replacement	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval
1	0.6	(0.5, 0.6)	0.7	(0.6, 0.8)	0.3	(0.2, 0.4)	0.4	(0.3, 0.5)
3	1.2	(1.1, 1.3)	1.4	(1.3, 1.6)	1.1	(1.0, 1.2)	1.5	(1.4, 1.7)
5	1.8	(1.7, 2.0)	2.2	(2.0, 2.4)	1.6	(1.5, 1.8)	2.3	(2.1, 2.6)
10	3.4	(3.1, 3.6)	4.6	(4.3, 5.0)	2.8	(2.5, 3.1)	4.5	(4.1, 4.9)
15	6.0	(5.5, 6.6)	8.3	(7.6, 9.1)	4.4	(3.9, 5.0)	7.1	(6.2, 8.1)

Table 3a Estimated subhazard of revision for Total Hip Replacement – Competing risks analysis

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
Gender						
Female (reference)	1.00			1.00		<0.001
Male	1.35	(1.23, 1.48)	<0.001	1.23	(1.10, 1.38)	
Age (years at THR)						
(per additional year)	0.970	(0.967, 0.973)	<0.001	0.971	(0.966, 0.975)	<0.001
BMI[a] (kg/m^2)						
(per additional unit)	1.030	(1.020, 1.041)	<0.001	1.020	(1.009, 1.032)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

Table 3b Estimated subhazard of revision for Total Knee Replacement – Competing risks analysis

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
Gender						
Female (reference)	1.00			1.00		
Male	1.54	(1.37, 1.72)	<0.001	1.51	(1.32, 1.73)	<0.001
Age (years at THR) (per additional year)	0.957	(0.952, 0.961)	<0.001	0.957	(0.951, 0.962)	<0.001
BMI[b] (kg/m^2) (per additional unit)	1.026	(1.013, 1.038)	<0.001	1.015	(1.002, 1.028)	0.023

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Table 4a Estimated hazard of revision for THR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
Gender						
Female (reference)	1.00			1.00		
Male	1.36	(1.24, 1.29)	<0.001	1.26	(1.13, 1.41)	<0.001
Age (years at THR)						
(per additional year)	0.978	(0.974, 0.983)	<0.001	0.977	(0.972, 0.982)	<0.001
BMI[a] (kg/m^2)						
(per additional unit)	1.029	(1.017, 1.040)	<0.001	1.019	(1.008, 1.031)	0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

Table 4b Estimated hazard of revision for TKR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
Gender						
Female (reference)	1.00			1.00		<0.001
Male	1.58	(1.41, 1.77)	<0.001	1.55	(1.36, 1.77)	
Age (years at THR)						
(per additional year)	0.962	(0.956, 0.967)	<0.001	0.961	(0.955, 0.968)	<0.001
BMI[a] (kg/m^2)						
(per additional unit)	1.024	(1.012, 1.037)	<0.001	1.015	(1.003, 1.028)	0.019

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Figure 1a Cumulative incidence estimate for revision of THR by body mass index

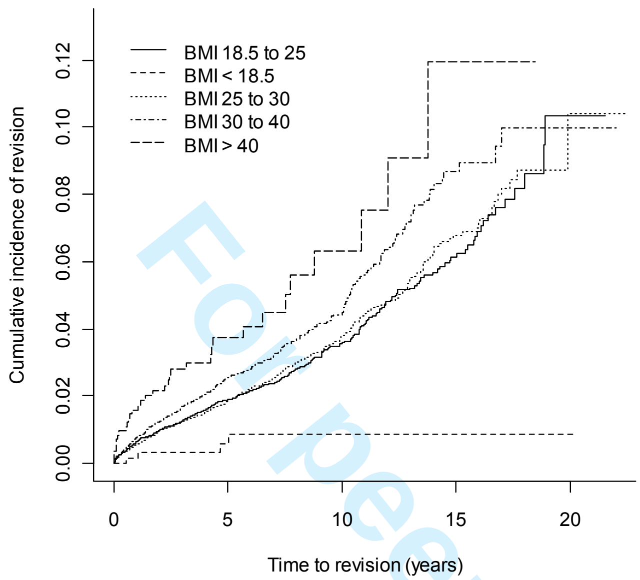


Figure 1b Cumulative incidence estimate for revision of TKR by body mass index

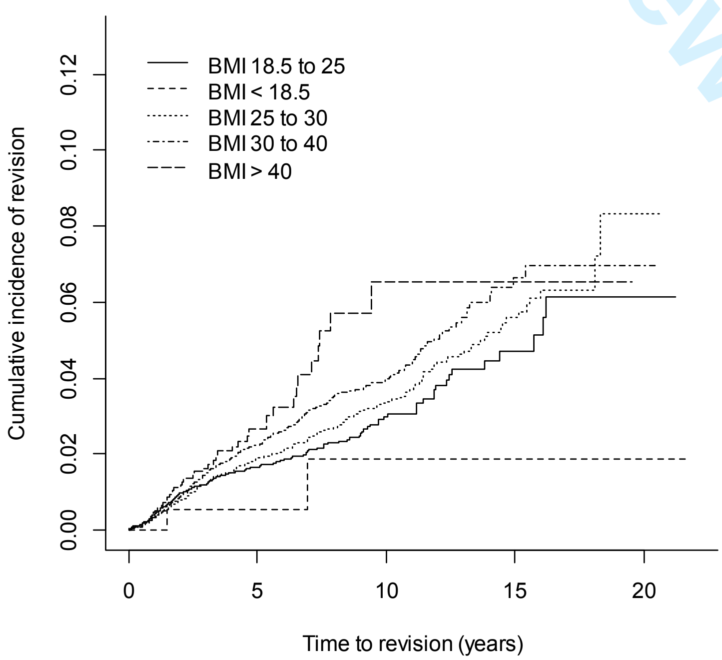


Figure 2a Cumulative incidence estimate for revision of THR by age

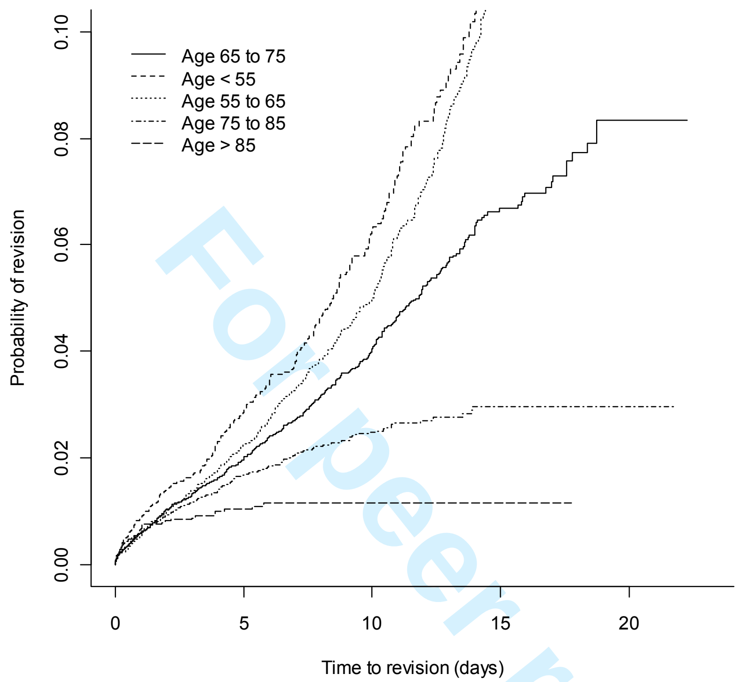
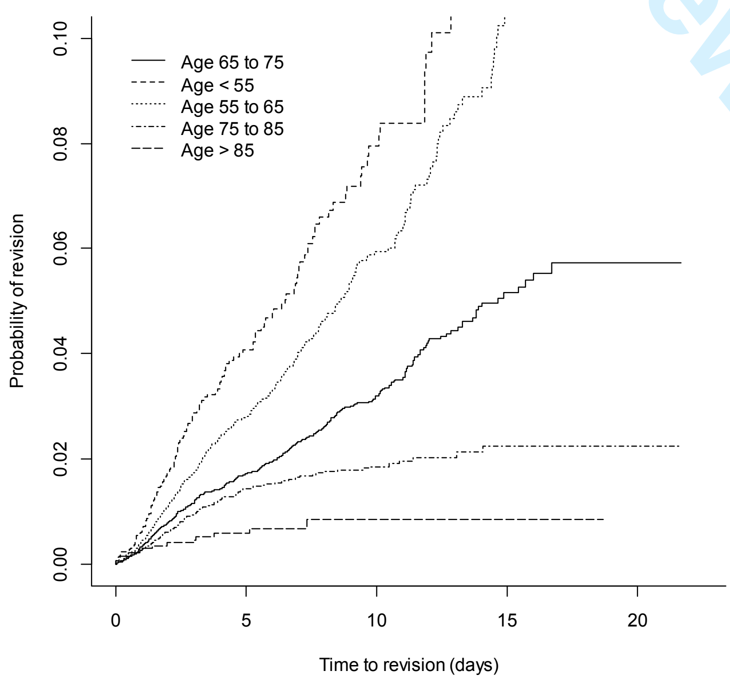


Figure 2b Cumulative incidence estimate for revision of TKR by age



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Population-based case cohort design (mentioned in Abstract/Method)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Competing risks survival (mentioned in Abstract/Method)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Age/gender available in National Joint Registry, but BMI has missing data. GPRD has good level of completeness for BMI.
Objectives	3	State specific objectives, including any prespecified hypotheses To provide population-based estimates for the effects of BMI on time to revision, with long follow-up (mentioned in Introduction).
Methods		
Study design	4	Present key elements of study design early in the paper Method of Fine and Gray referred to (top of Analysis subsection in Methods section)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Fully described in Participants subsubsection in Methods section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *"all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1991 until August 2011"*, quoted in the Participants subsubsection in Methods section.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable All defined in the Analysis subsection in Methods section: Outcome: time to first incidence of revision surgery, predictors: BMI, age, gender, potential confounders: smoking status, alcohol consumption, number of comorbid conditions.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group In the Analysis subsection in Methods section. Single group comprising those undergoing total replacement of the hip/knee (no controls).
Bias	9	Describe any efforts to address potential sources of bias In the Analysis subsection in Methods section. Comorbid conditions are a possible source of bias, hence the adjustment.
Study size	10	Explain how the study size was arrived at Population-based study. The GPRD is sized to enable precise estimates for most geographic/demographic subgroups.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why BMI was grouped according to WHO guidelines.

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done (in Analysis subsection in Methods section).
		(*b*) Describe any methods used to examine subgroups and interactions Two-way interactions examined (described in Analysis subsection in Methods section)
		(*c*) Explain how missing data were addressed Presence of BMI (in table 1) was sufficiently complete (>80% knees; >85% hips) and age and gender were 100% complete.
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable in such a dataset (most patients remained registered with the same GP in the GPRD, those leaving are not traceable).
		(*e*) Describe any sensitivity analyses Cox regression used as a sensitivity vs. Competing Risks Regression (described in Analysis subsection in Methods section).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Numbers given in table 1.
		(b) Give reasons for non-participation at each stage Not applicable (population-based data)
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Characteristics given in table 1.
		(b) Indicate number of participants with missing data for each variable of interest Given for BMI (the only variable of interest with missingness)
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time Number of revisions reported in table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Provided in tables 2, 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized Done (Results section; subsection entitled Survival Analysis)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not appropriate for this data, although we have provided estimates of numbers needed to "treat" (NNT).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done (Piecewise analysis and Cox regression – both documented in Results section; subsection entitled Survival Analysis)
Discussion		
Key results	18	Summarise key results with reference to study objectives Described in first few paragraphs of discussion.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

		Limitations covered in penultimate paragraph of discussion (e.g. lack of reliable indication data, long follow-up but includes older prostheses).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Covered in the middle part of the discussion section.
Generalisability	21	Discuss the generalisability (external validity) of the study results Population-based study so results are generalisable to the (gender-specific) UK adult population as a whole. Stated in 'Strengths and Limitations' subsection of Discussion section.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based NIHR Programme Grant for Applied Research grant number given in relevant section immediately following the discussion.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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A population-based survival analysis describing the association of body mass index on time to revision for total hip and knee replacements: Results from the UK General Practice Research Database

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Complete List of Authors:	Culliford, David; University of Southampton, Faculty of Medicine Maskell, Joe; University of Southampton, Public Health Sciences and Medical Statistics Judge, Andrew; University of Oxford, NIHR Musculoskeletal Biomedical Research Unit; University of Southampton, MRC Lifecourse Epidemiology Unit Arden, Nigel; University of Oxford, NIHR Musculoskeletal Biomedical Research Unit; University of Southampton, MRC Lifecourse Epidemiology Unit

Primary Subject Heading:	Epidemiology
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Keywords:	Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

A POPULATION-BASED SURVIVAL ANALYSIS DESCRIBING THE ASSOCIATION OF BODY MASS INDEX ON TIME TO REVISION FOR TOTAL HIP AND KNEE REPLACEMENTS: RESULTS FROM THE UK GENERAL PRACTICE RESEARCH DATABASE.

STUDY DESIGN: Population-based study.

AUTHORS' NAMES AND AFFILIATIONS

David Culliford (Senior Medical Statistician)[1]

Joe Maskell (Data Manager)[2]

Andy Judge (Senior Medical Statistician)[3,4]

Nigel K Arden (Professor of Rheumatic Diseases and Director)[3,4]

and the COAST Study group

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

ABSTRACT

Objectives Against a backdrop of rising levels of obesity, we describe and estimate associations of body mass index (BMI), age and gender with time to revision for subjects undergoing primary total hip (THR) or knee (TKR) replacement in the UK.

Design Population-based cohort study

Setting Routinely collected primary care data from a representative sample of general practices, including linked data on all secondary care events.

Participants Population-based cohort study of **63,162** THR and **54,276** TKR patients in the UK General Practice Research Database between 1988 and 2011.

Primary and secondary outcomes Risk of THR and TKR revision associated with BMI, age and gender, after adjusting for the competing risk of death.

Results The five-year cumulative incidence rate for THR was 2.2% for men and 1.8% for women (TKR: 2.3% for men, 1.6% for women). The adjusted overall subhazard ratios for THR patients undergoing subsequent hip revision surgery, with a competing risk of death, were estimated at 1.020 (95% CI: 1.009, 1.032) per additional unit (kg/m^2) of BMI, 1.23 (95% CI: 1.10, 1.38) for men compared with women and 0.970 (95% CI: 0.967, 0.973) per additional year of age. For TKR patients, the equivalent estimates were 1.015 (95% CI: 1.002, 1.028) for BMI; 1.51 (95% CI: 1.32, 1.73) for gender, and 0.957 (95% CI: 0.951, 0.962) for age. Morbidly obese THR patients had a 65.5% increase (95% CI: 15.4%, 137.3%, p=0.006) in the subhazard of revision versus the normal BMI group (18.5 to 25). The effect for TKR was smaller (a 43.9% increase) and weaker (95% CI: 2.6%, 103.9%, p=0.040).

Conclusions Body mass index is estimated to have a small but statistically significant association with the risk of hip and knee revision, but absolute numbers are small. Further studies are needed in order to distinguish between effects for specific revision surgery indications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Published revision rates for hip and knee replacement already exist, based on UK-based registry data, but follow-up periods are still relatively short.

Some evidence exists that obesity is a risk factor for undergoing primary total hip and knee replacements, but there is little in the literature for the risks of raised BMI on revision surgery.

The recording of BMI prior to primary total hip or knee replacement is less than complete in most national joint registries.

WHAT THIS STUDY ADDS

Body mass index is estimated to have a small positive association with the risk of hip and knee revision, after allowing for the competing risk of death.

The elevated risk of revision of the hip in morbidly obese (> 40 kg/m^2) patients during the first year after primary replacement is not observed in the knee.

It would take 175 TKR patients (152 for THR) to reduce their baseline BMI from obese to normal in order to prevent one revision operation after 5 years.

ARTICLE SUMMARY

Article focus

▪ Total joint replacement of the hip (THR) or knee (TKR) is commonly used as an intervention for patients with end-stage osteoarthritis of the lower limb.

▪ Joint prostheses sometimes require revision surgery and it is important for surgeons, patients and policy makers to understand the risk factors for time to revision.

▪ Although many studies modelling the time to joint revision have taken over the past 30 years, few such studies have been large-scale, population-based, competing risks analyses.

Key messages

▪ These data from the GPRD shows a small but significant association between body mass index and the time to revision for both hip and knee replacement.

▪ The risk of hip replacement revision for morbidly obese patients was two-thirds higher than for those with normal body mass index.

▪ The use of competing risks methods produced similar estimates of revision risk to those obtained using relative risks regression methods.

Strengths and potential limitations of the study

▪ The large sample size of the GPRD (over 5% of the UK general practice population) enables population-level inferences to be made

▪ The statistical methods explicitly account for the competing risk of death which has a much higher event rate than the event of interest (THR or TKR) in this patient group.

▪ GPRD data does not have directly linked information detailing the reasons for being referred for surgery, so we were unable to establish an exact indication.

INTRODUCTION

Total joint replacement of the hip and knee are well established as interventions for those suffering with end-stage osteoarthritis (OA) of the lower limb, with OA being the most frequent indication for total hip or knee replacement in the UK(1) (over 90% for hips and over 95% for knees). Yet hip and knee prostheses do not necessarily continue to function effectively for the lifetime of the patient(1, 2). Many traditional metal-on-polyethylene implants are likely to require revision surgery due to wear after 20 years of use due to wear characteristics and peri-prosthetic loosening. As a consequence, elective THR and TKR procedures have until relatively recently been indicated mainly in older patients, but even prostheses which make use of the latest technological developments (*e.g.* unicondylar knee prostheses) are not yet routinely recommended for use in younger patients.

A further dimension is added by the increasing prevalence of obesity in western populations, with clinicians in some cases considering patients too obese to undergo surgery(3, 4), partly due to the perceived increase in risk of both peri- and post-operative complications. There have also been examples of obese and/or morbidly obese patients experiencing restricted access to hip replacement surgery in some parts of the UK(5-7) where local healthcare planners have had similar concerns.

Revision procedures involve a surgical intervention to correct a prosthesis which is not functioning properly. Such operations are more costly than the original replacement procedure(8, 9) and are often more complex, with a higher level of risk to the patient. Population-based estimates of the time from primary surgery to a revision procedure are of importance to orthopaedic surgeons, rheumatologists, healthcare providers, policymakers and patients. Registry data, both in the U.K.(1) and internationally(10, 11), have been used extensively to estimate time to revision(12). Such data has been used previously to model prosthesis survival time in order to assess which specific demographic, clinical and prosthesis-specific factors are associated with time to failure(13, 14).

Over the 12 months to April 2011, there were over 178,000 total hip and knee replacement operations recorded in the National Joint Registry (NJR) for England and Wales(1). The NJR began recording data in 2003, and although it now contains virtually all replacements carried out in England and Wales, the maximum follow-up is currently less than ten years. The registry contains complete data on many variables, including age and gender, but body mass index is recorded in approximately 61% of subjects undergoing hip replacement (62% for knee). We chose to use data from a primary care database with long follow-up and UK-wide coverage.

The primary aim of this study was to use data from the General Practice Research Database to produce population-based estimates for the association of body mass index, age and gender with the time to revision surgery in the long term following a THR or TKR.

METHOD

Participants

We used data from the General Practice Research Database (GPRD). The GPRD comprises the entire computerized medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from over 600 contributing practices chosen to be representative of the wider UK population(15). GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD has recently become part of the new Clinical Practice Research Datalink (CPRD) which is administered by the Medicines and Healthcare products Regulatory Agency (MHRA).

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. The GPRD comprises entire general practice populations rather than probability-based samples of patients.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1991 until August 2011. We then identified any secondary (revision) hip or knee operations for these patients which occurred subsequent to the primary operation. The list of Read codes used to identify the primary and revision operations were independently reviewed by different clinicians and a consensus list agreed between them. Deaths recorded within the GPRD were also identified. The date of the first incidence of a subject's hip or knee replacement was used as the start time. The event of interest in all time-to-event models was the first recorded revision operation. Censoring events were the end of study date (11th August 2011) or the transfer of a patient out of the GPRD for any reason other than death. Death from any cause was treated as a competing risk in the primary analysis. Patients were included in the analysis if aged 18 years or over at the time of the replacement operation. Participant demographics including age, gender, pre-operative body mass index (BMI), smoking and drinking status were collated, in addition to information on comorbid conditions.

Analysis

We used the competing risks regression methods of Fine and Gray(16) to estimate the effects of a subject's body mass index (BMI), age and gender on the time to revision of a prosthesis implanted during a THR or TKR operation. The substantive event of interest was the first incidence of revision surgery, with all-cause mortality separately identified as a competing risk. The rationale for using competing risks regression is that methods which treat death as just another censoring event may overestimate risk for an event of interest, especially in an older population(17). We adjusted for a range of important covariates and potential confounders: smoking status, alcohol consumption and the number of comorbid conditions (which include diabetes, hypertension, stroke, cardiovascular disease and anaemia). All covariates were treated as fixed at baseline. Analyses for hips and knees were performed separately, with prosthesis survival at the end of follow-up being of primary interest. Proportionality of hazards assumptions was assessed by examining complementary log-log plots of the cumulative incidence. As a sensitivity analysis we modelled the same data using standard methods which do not cater for competing risks (*i.e.* Cox regression analysis with death as a censoring event). We also calculated stand-alone estimates for the cumulative incidence of revision surgery at 1, 5, 10 and 15 years, and plotted estimates of the age-, gender- and BMI-specific cumulative incidence curves for the whole cohort.

All tests of significance were at the 5% level and two-sided. Interval estimates were based on 95% confidence intervals. The main statistical analysis was carried out using R (R Core Team, 2012. R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.2 (SAS Institute Inc., Cary, NC) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX).

RESULTS

Participant demographics

Over the study period the database contained 63,162 patients undergoing total hip replacement and 54,276 patients undergoing total knee replacement. The average age at replacement was similar in both the THR and the TKR groups but the proportion of women was greater for both THR and TKR (table 1). For those with a recorded pre-operative BMI, the proportion of obese subjects (BMI >=30 kg/m^2) was 26.2% for THR and 39.8% for TKR and the proportion of morbidly obese subjects (which we define as having a BMI >=40 kg/m^2) was 1.6% for THR and 3.6% for TKR. Eighty percent of pre-operative BMI values used were recorded within five years of the primary operation. Table 1 describes the baseline characteristics of the cohort, including summary statistics and missing data percentages for all explanatory variables where complete data was not observed.

Survival analysis

The estimated cumulative incidence of revision at five years was 2.0% (95% CI: 1.8, 2.1) for THR and 1.9% (95% CI: 1.8, 2.1) for TKR. For women, cumulative incidence at five years was 1.8% (95% CI: 1.7, 2.0) for THR and 1.6% (95% CI: 1.5, 1.8) for TKR, and for men 2.2% (95% CI: 2.0, 2.4) and 2.3% (95% CI: 2.1, 2.6) respectively. Table 2 provides gender-specific estimates of cumulative incidence with point-wise confidence intervals for a range of times (1, 3, 5, 10 and 15 years after THR/TKR). Figures 1 and 2 provide a further breakdown of the cumulative incidence of revision for the whole THR and TKR cohorts respectively, with separate incidence curves for categorised BMI (figure 1) and categorised age (figure 2). Gray's test was used to examine whether there were differences in the overall cumulative incidence of revision by gender, categorised age (<55, 55-64, 65-74, 75-84, >85 years) and categorised BMI (<18.5, 18.5-24.9, 25-29.9, 30-39.9, >40 kg/m^2). All three variables showed statistically significant differences in cumulative incidence for both hip (Gray's test statistic: gender, age, BMI, p<0.001 for all) and knee (Gray's test statistic: gender, age, BMI, p<0.001 for all).

In a single predictor (univariable) survival model allowing for the competing risk of death over the entire period of follow-up, we estimated that THR subjects had a 3.0% increase in the subhazard of revision (SHR: 1.030, 95% CI: 1.020, 1.041, p<0.001) for each extra unit (kg/m^2) of BMI, with TKR subjects showing a 2.6% increase per unit (SHR: 1.026, 95% CI: 1.013, 1.038, p<0.001). The subhazard of revision was significantly greater for men compared to women for both THR (subhazard ratio [SHR]: 1.35, 95% CI: 1.23, 1.48, p<0.001) and TKR 2.0% (SHR: 1.54, 95% CI: 1.37, 1.72, p<0.001). Age at total joint replacement was also a significant univariable predictor of revision for both hip and knee, with THR subjects estimated to have a 3% reduction in the subhazard of revision (SHR: 0.970, 95% CI: 0.967, 0.973, p<0.001) for each extra year of age, with TKR subjects showing a 4.3% reduction (SHR: 0.957, 95% CI: 0.952, 0.961, p<0.001).

The effects for all three variables (gender, age and BMI) were then estimated in multivariable competing risks regression models after adjusting for smoking status, drinking status and the number of comorbid conditions, again over the entire period of follow-up. For age, the estimates for the subhazard of revision were almost exactly the same as those from the univariable model for both hip and knee, but for gender (SHR: 1.23 for hip; 1.51 for knee) and BMI (SHR: 1.020 for hip; 1.015 for knee) the estimates were smaller. Nevertheless, all three variables remained statistically significant for both hip and knee in the presence of adjustment. For a five-unit and ten-unit increase in BMI, this represents an increase in THR revision risk of 10.4% and 21.9% respectively (7.7% and 16.1% for TKR).Testing for two-way interactions between age, gender and BMI did not produce any significant effects. All subhazard estimates (with 95% confidence intervals and p-values) from the univariable and multivariable models are given in table 3.

To further explore the effect estimates for BMI we ran the same adjusted age-gender-BMI model described above, but used categorical BMI instead of continuous. For morbidly obese TKR subjects (BMI 40+) there was a 43.9% increase (95% CI: 2.6%, 103.9%, p=0.040) in the subhazard of revision compared to those with a normal BMI (18.5 to 25), but the effect for THR was larger (a 65.5% increase) and stronger (95% CI: 15.4%, 137.3%, p=0.006). The effect sizes were similar to those obtained when using the adjusted subhazard ratio estimate of continuous BMI for a subject with a BMI of 45 relative to one with a BMI of 22 (increase of 57.7% for THR; 40.8% for TKR). For obese patients in the range 30 to 40 kg/m^2 versus those with a normal BMI, the estimated subhazard ratio for revision was weakly significant for THR (15.7% increase, 95% CI: 0.2%, 33.7%, p=0.048) but not for TKR (17.9% increase, 95% CI: -1.9%, 41.6%, p=0.079).

As a sensitivity analysis, we also performed standard Cox regressions with revision surgery as the event of interest and where no distinction was made between death and other censoring events. Univariable models for age, gender and BMI gave very similar results to the competing risks analysis, as did the multivariable models which adjusted for the same factors as in the competing risks regression. Results from the Cox regression models are given in table 4. In addition, we calculated that it would take 175 TKR patients to reduce their baseline BMI from obese to normal in order to prevent one revision operation after 5 years. For THR patients this number reduces to 152.

Finally, we assessed whether the higher incidence of hip revision surgery during the first year following THR (see figures 1a and 2a) might compromise the proportionality assumption and therefore suggest the inclusion of time-dependent effects. Separate univariable piecewise competing risks models for hip revision were fitted for gender, age (<= 65 years vs. > 65) and BMI (> 40 vs. <= 40). A single changepoint at one year was used to simultaneously estimate two subhazard ratios for revision (before and after one year following THR). The only model which provided some evidence for a different subhazard ratio during the first year was with BMI (> 40 vs. <= 40) as the predictor (SHR: 2.619, 95% CI: 1.502, 4.560, p=0.001), but this was not matched with a statistically significant estimate for revision after the first year (SHR: 0.575, 95% CI: 0.238, 1.170, p=0.130).

DISCUSSION

This study presents population-based estimates for the risk of revision following total joint replacement of the hip and knee using methods from survival analysis. Cumulative incidence rates of revision were higher for men than for women and higher for hips than knees. Age, gender and body mass index were estimated to be significant predictors of time to revision in an adjusted model allowing for the competing risk of death. Severely obese patients undergoing total hip replacement were observed to have a higher risk of revision surgery during the first year following replacement, but the same effect was not observed for knee replacement.

The literature on obesity as a risk factor for hip and knee arthroplasty concentrates mainly on the risk for primary replacement rather than for revision procedures, and most use rate differences to estimate relative risk, rather than using time-to-event methods. Many published studies are small and do not have sufficient power to detect rare outcomes. Often these studies are locally based and the generalisability to population level is questionable. Mostly results are presented for categorised BMI, which is often dichotomised at 30 kg/m^2, and where results for the morbidly obese are reported, the sample size is small.

One of the largest studies examining primary replacement followed up a cohort of over 490,000 middle-aged women over an average of 2.9 years and found increased incidence of hip and knee replacement in obese subjects(18). Of the studies which consider the effect of obesity on outcomes after primary joint replacement, several focus mainly on events such as complications arising from surgery(19) or subsequent admission to an intensive care unit(20), rather than the time to revision surgery. Among studies of other non-revision outcomes, Andrew *et al*(21) looked at the change in Oxford Hip Score five years after THR and found no difference between non-obese, obese and morbidly obese patients, but in a smaller study(22) using Harris Hip Score (HHS) with the same length of follow-up, an increase in BMI was associated with a small but significant reduction in HHS.

An editorial on obesity and joint replacement in 2006(23) suggested that it is those with a BMI of greater than 40 units (rather than 30) who are at risk of worse outcomes, yet several subsequent studies have used a BMI cut-point of 30 kg/m^2. A recent Australian study of 2026 THR and 535 TKR patients found no difference in mid-term survival rates between the obese (BMI > 30 kg/m^2) and non-obese(24). Another study from Switzerland used Cox regression to estimate the risk of revision in 2495 THRs using the same cut-point for BMI, estimating a non-significant adjusted hazard ratio for revision of 2.2 (95% CI: 0.9 to 5.3) for obese versus non-obese patients(19). However, a recent Canadian study of 3290 THRs did categorise BMI to include a morbidly obese group (BMI > 40 kg/m^2) and although the authors found no difference in time to revision between BMI categories in an unadjusted analysis, there was a marginally significant difference for septic revisions(25).

Our results suggest that there may be a 1.5% to 2% rise in the risk of knee and hip revision respectively for each extra unit of BMI. However, there is some variation in risk across the entire range of observed BMI values. For hips, there appears to be very little difference in BMI-related risk between the normal weight and overweight categories. However, figure 1a shows that for hips there may be a revision rate of approximately 6% for the morbidly obese after 10 years, against a 3% rate for the normal and overweight. For knees, figure 1b shows a more even distribution across the BMI categories up to about 7 years after TKR, but with higher risk for the morbidly obese between 7 and 10 years after TKR.

Although recommendations(26, 27) to consider the use of the cumulative incidence function for analysing prosthesis survival are gaining acceptance(28), the use of competing risks regression to model associated risk factors is still not widely observed. The justification for using competing risks methods in our primary analysis is that hip and knee prostheses are mainly implanted in older patients for whom mortality is a substantial competing risk which may be several times greater than the risk of revision. What is perhaps surprising is that our results show little difference between the hazard and subhazard ratio estimates from the Cox and the competing risks regression models respectively, although the former has a cause-specific interpretation with no distinction between death and censoring whereas the latter directly models the cumulative incidence of revision.

Strengths and potential limitations of the study

The strengths of the study data more than make up for its limitations. GPRD data has individual date-stamped records of patient event data in primary and secondary care settings, including data on many potential confounders, including comorbidities, BMI, smoking and drinking. The GPRD practice network covers all of the United Kingdom, and approximately 5% of all practices are covered by the GPRD. The high degree of generalisability afforded by this very large sample enables population-level inferences to be made. Follow-up is long, with several hundred prostheses in the dataset having over 20 years of follow-up without being revised. The choice of the statistical methods used to allow for the competing risk of death adds a further degree of robustness to the study. The regression estimates of the hazard ratio for body mass index as a factor associated with revision benefit from a precision which is not usually achievable outside of national registers, especially for the group of morbidly obese patients within which event rates in the literature are low.

There are several limitations to this work. The revision rate estimates hip and knee at 5 years are close to, but slightly less than those reported by the National Joint Registry, but the GPRD data used in this study includes prostheses implanted from the late 1980s. Also our data does not have directly linked information on the indication for surgery, which would have been enabled a sub-analysis by reason for revision. Although certain indications for revision are more common than others depending on follow-up time (e.g. infection occurring early), any inferences about indication-specific risks before or after a given follow-up time would not have been reliable.

CONCLUSION

This study has presented estimates of rates and risk factors for revision surgery on hip and knee prostheses using one of the largest available population-based sets of joint replacement data outside of national arthroplasty registries. Our estimates suggest that body mass index is positively associated with the risk of hip and knee revision, but studies of register data linked with sources of demographic and clinical data are needed in order to distinguish between effects for specific indications for revision surgery.

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Author affiliations

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

Collaborators The following people are members of the COAST Study group: Cyrus Cooper, Mark Mullee, James Raftery, Andrew Carr, Andrew Price, Kassim Javaid, David Beard, Douglas Altman, Nicholas Clarke, Jeremy Latham, Sion Glyn-Jones and David Barrett.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Prof. Arden had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Culliford, Judge and Arden.

Acquisition of data: Arden.

Analysis and interpretation of data: Culliford, Maskell, Judge and Arden.

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Table 1 Clinical and Demographic characteristics – all subjects undergoing Total Hip or Knee Replacement

	Total Hip Replacement (N=63,162)		**Total Knee Replacement** (N=54,276)	
	Female (N=39,292)	Male (N=23,870)	Female (N=31,682)	Male (N=22,594)
Age (mean, SD)	70.5 (11.1)	67.7 (11.0)	70.7 (9.6)	69.4 (9.4)
Gender (%)	62.2	37.8	58.3	41.6
BMI (mean, SD)	27.2 (5.1)	27.7 (4.3)	29.6(5.6)	28.8(4.4)
Missing BMI (%)	19.1	19.3	13.8	14.0
Revisions (N, %)	1000 (2.55)	811 (3.40)	572 (1.8)	614 (2.7)
Deaths pre-revision (N, %)	6615 (16.8)	4201 (17.6)	4110(13.0)	3349 (14.8)
Number of comorbid conditions (%):				
0	42.8%	48.1%	37.5%	43.7%
1	34.2%	31.0%	37.4%	35.8%
2+	23.0%	20.9%	25.2%	20.6%

Table 2 Cumulative incidence rates for revision surgery at selected times following THR and TKR

	Hip				Knee			
	Female		Male		Female		Male	
Years since total joint replacement	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval
1	0.6	(0.5, 0.6)	0.7	(0.6, 0.8)	0.3	(0.2, 0.4)	0.4	(0.3, 0.5)
3	1.2	(1.1, 1.3)	1.4	(1.3, 1.6)	1.1	(1.0, 1.2)	1.5	(1.4, 1.7)
5	1.8	(1.7, 2.0)	2.2	(2.0, 2.4)	1.6	(1.5, 1.8)	2.3	(2.1, 2.6)
10	3.4	(3.1, 3.6)	4.6	(4.3, 5.0)	2.8	(2.5, 3.1)	4.5	(4.1, 4.9)
15	6.0	(5.5, 6.6)	8.3	(7.6, 9.1)	4.4	(3.9, 5.0)	7.1	(6.2, 8.1)

Table 3a Estimated subhazard of revision for Total Hip Replacement – Competing risks analysis

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m^2)						
(per additional unit)	1.030	(1.020, 1.041)	<0.001	1.020	(1.009, 1.032)	<0.001
Gender						
Female (reference)	1.00			1.00		
Male	1.35	(1.23, 1.48)	<0.001	1.23	(1.10, 1.38)	<0.001
Age (years at THR)						
(per additional year)	0.970	(0.967, 0.973)	<0.001	0.971	(0.966, 0.975)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

Table 3b Estimated subhazard of revision for Total Knee Replacement – Competing risks analysis

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[b] (kg/m^2) (per additional unit)	1.026	(1.013, 1.038)	<0.001	1.015	(1.002, 1.028)	0.023
Gender						
Female (reference)	1.00			1.00		<0.001
Male	1.54	(1.37, 1.72)	<0.001	1.51	(1.32, 1.73)	
Age (years at THR) (per additional year)	0.957	(0.952, 0.961)	<0.001	0.957	(0.951, 0.962)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Table 4a Estimated hazard of revision for THR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m^2)						
(per additional unit)	1.029	(1.017, 1.040)	<0.001	1.019	(1.008, 1.031)	0.001
Gender						
Female (reference)	1.00			1.00		
Male	1.36	(1.24, 1.29)	<0.001	1.26	(1.13, 1.41)	<0.001
Age (years at THR)						
(per additional year)	0.978	(0.974, 0.983)	<0.001	0.977	(0.972, 0.982)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

Table 4b Estimated hazard of revision for TKR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m^2) (per additional unit)	1.024	(1.012, 1.037)	<0.001	1.015	(1.003, 1.028)	0.019
Gender						
Female (reference)	1.00			1.00		
Male	1.58	(1.41, 1.77)	<0.001	1.55	(1.36, 1.77)	<0.001
Age (years at THR) (per additional year)	0.962	(0.956, 0.967)	<0.001	0.961	(0.955, 0.968)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Figure legends

Figure 1a Cumulative incidence estimate for revision of THR by body mass index

Figure 1b Cumulative incidence estimate for revision of TKR by body mass index

Figure 2a Cumulative incidence estimate for revision of THR by age

Figure 2b Cumulative incidence estimate for revision of TKR by age

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1

A POPULATION-BASED SURVIVAL ANALYSIS DESCRIBING THE ASSOCIATION OF BODY MASS INDEX ON TIME TO REVISION FOR TOTAL HIP AND KNEE REPLACEMENTS: RESULTS FROM THE UK GENERAL PRACTICE RESEARCH DATABASE.

STUDY DESIGN: Population-based study.

AUTHORS' NAMES AND AFFILIATIONS

David Culliford (Senior Medical Statistician)[1]

Joe Maskell (Data Manager)[2]

Andy Judge (Senior Medical Statistician)[3,4]

Nigel K Arden (Professor of Rheumatic Diseases and Director)[3,4]

and the COAST Study group

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

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ABSTRACT

Objectives Against a backdrop of rising levels of obesity, we describe and estimate associations of body mass index (BMI), age and gender with time to revision for subjects undergoing primary total hip (THR) or knee (TKR) replacement in the UK.

Design Population-based cohort study

Setting Routinely collected primary care data from a representative sample of general practices, including linked data on all secondary care events.

Participants Population-based cohort study of **63,162** THR and **54,276** TKR patients in the UK General Practice Research Database between 1988 and 2011.

Primary and secondary outcomes Risk of THR and TKR revision associated with BMI, age and gender, after adjusting for the competing risk of death.

Results The five-year cumulative incidence rate for THR was 2.2% for men and 1.8% for women (TKR: 2.3% for men, 1.6% for women). The ~~estimated~~ adjusted overall subhazard ratios for THR patients undergoing subsequent hip revision surgery, with a competing risk of death, were estimated at 1.020 (95% CI: 1.009, 1.032) per additional unit (kg/m^2) of BMI, 1.23 (95% CI: 1.10, 1.38) for men compared with women and 0.970 (95% CI: 0.967, 0.973) per additional year of age. For TKR patients, the equivalent estimates were 1.015 (95% CI: 1.002, 1.028) for BMI; 1.51 (95% CI: 1.32, 1.73) for gender, and 0.957 (95% CI: 0.951, 0.962) for age. Morbidly obese THR patients had a 65.5% increase (95% CI: 15.4%, 137.3%, p=0.006) in the subhazard of revision versus the normal BMI group (18.5 to 25).

The effect for TKR was smaller (a 43.9% increase) and weaker (95% CI: 2.6%, 103.9%, p=0.040).

Conclusions Body mass index is estimated to have a small but statistically significant association with the risk of hip and knee revision, but absolute numbers are small. Further studies are needed in order to distinguish between effects for specific revision surgery indications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Published revision rates for hip and knee replacement already exist, based on UK-based registry data, but follow-up periods are still relatively short.

Some evidence exists that obesity is a risk factor for undergoing primary total hip and knee replacements, but there is little in the literature for the risks of raised BMI on revision surgery.

The recording of BMI prior to primary total hip or knee replacement is less than complete in most national joint registries.

WHAT THIS STUDY ADDS

Body mass index is estimated to have a small positive association with the risk of hip and knee revision, after allowing for the competing risk of death.

The elevated risk of revision of the hip in morbidly obese (> 40 kg/m^2) patients during the first year after primary replacement is not observed in the knee.

It would take 175 TKR patients (152 for THR) to reduce their baseline BMI from obese to normal in order to prevent one revision operation after 5 years.

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ARTICLE SUMMARY

Article focus

▪ Total joint replacement of the hip (THR) or knee (TKR) is commonly used as an intervention for patients with end-stage osteoarthritis of the lower limb.

▪ Joint prostheses sometimes require revision surgery and it is important for surgeons, patients and policy makers to understand the risk factors for time to revision.

▪ Although many studies modelling the time to joint revision have taken over the past 30 years, few such studies have been large-scale, population-based, competing risks analyses.

Key messages

▪ These data from the GPRD shows a small but significant association between body mass index and the time to revision for both hip and knee replacement.

▪ The risk of hip replacement revision for morbidly obese patients was two-thirds higher than for those with normal body mass index.

▪ The use of competing risks methods produced similar estimates of revision risk to those obtained using relative risks regression methods.

Strengths and potential limitations of the study

▪ The large sample size of the GPRD (over 5% of the UK general practice population) enables population-level inferences to be made

▪ The statistical methods explicitly account for the competing risk of death which has a much higher event rate than the event of interest (THR or TKR) in this patient group.

▪ GPRD data does not have directly linked information detailing the reasons for being referred for surgery, so we were unable to establish an exact indication.

INTRODUCTION

Total joint replacement of the hip and knee are well established as interventions for those suffering with end-stage osteoarthritis (OA) of the lower limb, with OA being the most frequent indication for total hip or knee replacement in the UK(1) (over 90% for hips and over 95% for knees). Yet hip and knee prostheses do not necessarily continue to function effectively for the lifetime of the patient(1, 2). Many traditional metal-on-polyethylene implants are likely to require revision surgery due to wear after 20 years of use due to wear characteristics and peri-prosthetic loosening. As a consequence, elective THR and TKR procedures have until relatively recently been indicated mainly in older patients, but even prostheses which make use of the latest technological developments (*e.g.* unicondylar knee prostheses) are not yet routinely recommended for use in younger patients.

A further dimension is added by the increasing prevalence of obesity in western populations, with clinicians in some cases considering patients too obese to undergo surgery(3, 4), partly due to the perceived increase in risk of both peri- and post-operative complications. There have also been examples of obese and/or morbidly obese patients experiencing restricted access to hip replacement surgery in some parts of the UK(5-7) where local healthcare planners have had similar concerns.

Revision procedures involve a surgical intervention to correct a prosthesis which is not functioning properly. Such operations are more costly than the original replacement procedure(8, 9) and are often more complex, with a higher level of risk to the patient. Population-based estimates of the time from primary surgery to a revision procedure are of

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importance to orthopaedic surgeons, rheumatologists, healthcare providers, policymakers and patients. Registry data, both in the U.K.(1) and internationally(10, 11), have been used extensively to estimate time to revision(12). Such data has been used previously to model prosthesis survival time in order to assess which specific demographic, clinical and prosthesis-specific factors are associated with time to failure(13, 14).

Over the 12 months to April 2011, there were over 178,000 total hip and knee replacement operations recorded in the National Joint Registry (NJR) for England and Wales(1). The NJR began recording data in 2003, and although it now contains virtually all replacements carried out in England and Wales, the maximum follow-up is currently less than ten years. However, although TThe registry contains complete data on many variables, including age and gender, but body mass index is recorded in approximately 61% of subjects undergoing hip replacement (62% for knee). We chose to use data from a primary care database with long follow-up and UK-wide coverage.

The primary aim of this study was to use data from the General Practice Research Database to produce population-based estimates for the association of body mass index, age and gender with the time to revision surgery in the long term following a THR or TKR.

METHOD

Participants

We used data from the General Practice Research Database (GPRD). The GPRD comprises the entire computerized medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from over 600 contributing practices chosen to be representative of the wider UK population(15). GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD has recently become part of the new Clinical Practice Research Datalink (CPRD) which is administered by the Medicines and Healthcare products Regulatory Agency (MHRA).

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. The GPRD comprises entire general practice populations rather than probability-based samples of patients.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1991 until August 2011. We then identified any secondary (revision) hip or knee operations for these patients which occurred subsequent to the primary operation. The list of Read codes used to identify the primary and revision operations were independently reviewed by different clinicians and a consensus list agreed between them. Deaths recorded within the GPRD were also identified. The date of the first incidence of a subject's hip or knee replacement was used as the start time. The event of interest in all time-to-event models was the first recorded revision operation. Censoring events were the end of study date (11th August 2011) or the transfer of a patient out of the GPRD for any reason other than death. Death from any cause was treated as a competing risk in the primary analysis. Patients were included in the analysis if aged 18 years or over at the time of the replacement operation. Participant demographics including age, gender,

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pre-operative body mass index (BMI), smoking and drinking status were collated, in addition to information on comorbid conditions.

Analysis

We used the competing risks regression methods of Fine and Gray(16) to estimate the effects of a subject's body mass index (BMI), age and gender on the time to revision of a prosthesis implanted during a THR or TKR operation. The substantive event of interest was the first incidence of revision surgery, with all-cause mortality separately identified as a competing risk. The rationale for using competing risks regression is that methods which treat death as just another censoring event may overestimate risk for an event of interest, especially in an older population(17). We adjusted for a range of important covariates and potential confounders: smoking status, alcohol consumption and the number of comorbid conditions (which include diabetes, hypertension, stroke, cardiovascular disease and anaemia). All covariates were treated as fixed at baseline. Analyses for hips and knees were performed separately, with prosthesis survival at the end of follow-up being of primary interest. Proportionality of hazards assumptions was assessed by examining complementary log-log plots of the cumulative incidence. As a sensitivity analysis we modelled the same data using standard methods which do not cater for competing risks (*i.e.* Cox regression analysis with death as a censoring event). We also calculated stand-alone estimates for the cumulative incidence of revision surgery at 1, 5, 10 and 15 years, and plotted estimates of the age-, gender- and BMI-specific cumulative incidence curves for the whole cohort.

All tests of significance were at the 5% level and two-sided. Interval estimates were based on 95% confidence intervals. The main statistical analysis was carried out using R (R Core Team, 2012. R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.2 (SAS

Institute Inc., Cary, NC) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX).

RESULTS

Participant demographics

Over the study period the database contained 63,162 patients undergoing total hip replacement and 54,276 patients undergoing total knee replacement. The average age at replacement was similar in both the THR and the TKR groups but the proportion of women was greater for both THR and TKR (table 1). For those with a recorded pre-operative BMI, the proportion of obese subjects (BMI >=30 kg/m^2) was 26.2% for THR and 39.8% for TKR and the proportion of morbidly obese subjects (which we define as having a BMI >=40 kg/m^2) was 1.6% for THR and 3.6% for TKR. Eighty percent of pre-operative BMI values used were recorded within five years of the primary operation. Table 1 describes the baseline characteristics of the cohort, including summary statistics and missing data percentages for all explanatory variables where complete data was not observed.

Survival analysis

The estimated cumulative incidence of revision at five years was 2.0% (95% CI: 1.8, 2.1) for THR and 1.9% (95% CI: 1.8, 2.1) for TKR. For women, cumulative incidence at five years was 1.8% (95% CI: 1.7, 2.0) for THR and 1.6% (95% CI: 1.5, 1.8) for TKR, and for men 2.2% (95% CI: 2.0, 2.4) and 2.3% (95% CI: 2.1, 2.6) respectively. Table 2 provides gender-specific estimates of cumulative incidence with point-wise confidence intervals for a range of times (1, 3, 5, 10 and 15 years after THR/TKR). Figures 1 and 2 provide a further breakdown of the cumulative incidence of revision for the whole THR and TKR cohorts respectively, with separate incidence curves for categorised BMI (figure 1) and categorised age (figure 2). Gray's test was used to examine whether there were ~~overall~~ differences in the overall cumulative incidence of revision by gender, categorised age (<55, 55-64, 65-74, 75-84, >85 years) and categorised BMI (<18.5, 18.5-24.9, 25-29.9, 30-39.9, >40 kg/m^2). All three variables showed statistically significant differences in cumulative incidence for both hip (Gray's test statistic: gender, age, BMI, p<0.001 for all) and knee (Gray's test statistic: gender, age, BMI, p<0.001 for all).

In a single predictor (univariable) survival model allowing for the competing risk of death over the entire period of follow-up, we estimated that THR subjects had a 3.0% increase in the subhazard of revision (SHR: 1.030, 95% CI: 1.020, 1.041, p<0.001) for each extra unit (kg/m^2) of BMI, with TKR subjects showing a 2.6% increase per unit (SHR: 1.026, 95% CI: 1.013, 1.038, p<0.001). ~~found that t~~The subhazard of revision was significantly greater for men compared to women for both THR (subhazard ratio [SHR]: 1.35, 95% CI: 1.23, 1.48, p<0.001) and TKR 2.0% (SHR: 1.54, 95% CI: 1.37, 1.72, p<0.001). Age at total joint replacement was also a significant univariable predictor of revision for both hip and knee, with THR subjects estimated to have a 3% reduction in the subhazard of revision (SHR: 0.970, 95% CI: 0.967, 0.973, p<0.001) for each extra year of age, with TKR subjects showing a 4.3% reduction (SHR: 0.957, 95% CI: 0.952, 0.961, p<0.001). ~~The univariable model for body mass index estimated that THR subjects had a 3.0% increase in the subhazard of revision (SHR: 1.030, 95% CI: 1.020, 1.041, p<0.001) for each extra unit (kg/m^2) of BMI, with TKR subjects showing a 2.6% increase per unit (SHR: 1.026, 95% CI: 1.013, 1.038, p<0.001).~~

The effects for all three variables (gender, age and BMI) were then estimated in multivariable competing risks regression models after adjusting for smoking status, drinking status and the number of comorbid conditions, again over the entire period of follow-up. For age, the estimates for the subhazard of revision were almost exactly the same as those from the univariable model for both hip and knee, but for gender (SHR: 1.23 for hip; 1.51 for knee) and BMI (SHR: 1.020 for hip; 1.015 for knee) the estimates were smaller. Nevertheless, all three variables remained statistically significant for both hip and knee in the presence of adjustment. For a five-unit and ten-unit increase in BMI, this represents an increase in THR revision risk of 10.4% and 21.9% respectively (7.7% and 16.1% for TKR). Testing for two-way interactions between age, gender and BMI did not produce any significant effects. All subhazard estimates (with 95% confidence intervals and p-values) from the univariable and multivariable models are given in table 3.

To further explore the effect estimates for BMI we ran the same adjusted age-gender-BMI model described above, but used categorical BMI instead of continuous. For morbidly obese TKR subjects (BMI 40+) there was a 43.9% increase (95% CI: 2.6%, 103.9%, p=0.040) in the subhazard of revision compared to those with a normal BMI (18.5 to 25), but the effect for THR was larger (a 65.5% increase) and stronger (95% CI: 15.4%, 137.3%, p=0.006). The effect sizes were similar to those obtained when using the adjusted subhazard ratio estimate of continuous BMI for a subject with a BMI of 45 relative to one with a BMI of 22 (increase of 57.7% for THR; 40.8% for TKR). For obese patients in the range 30 to 40 kg/m^2 versus those with a normal BMI, the estimated subhazard ratio for revision was weakly significant for THR (15.7% increase, 95% CI: 0.2%, 33.7%, p=0.048) but not for TKR (17.9% increase, 95% CI: -1.9%, 41.6%, p=0.079).

As a sensitivity analysis, we also performed standard Cox regressions with revision surgery as the event of interest and where no distinction was made between death and other censoring events. Univariable models for age, gender and BMI gave very similar results to the competing risks analysis, as did the multivariable models which adjusted for the same factors as in the competing risks regression. Results from the Cox regression models are given in table 4. In addition, we calculated that it would take 175 TKR patients to reduce

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their baseline BMI from obese to normal in order to prevent one revision operation after 5 years. For THR patients this number reduces to 152.

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Finally, we assessed whether the higher incidence of hip revision surgery during the first year following THR (see figures 1a and 2a) might compromise the proportionality assumption and therefore suggest the inclusion of time-dependent effects. Separate univariable piecewise competing risks models for hip revision were fitted for gender, age (<= 65 years vs. > 65) and BMI (> 40 vs. <= 40). A single changepoint at one year was used to simultaneously estimate two subhazard ratios for revision (before and after one year following THR). The only model which provided some evidence for a different subhazard ratio during the first year was with BMI (> 40 vs. <= 40) as the predictor (SHR: 2.619, 95% CI: 1.502, 4.560, p=0.001), but this was not matched with a statistically significant estimate for revision after the first year (SHR: 0.575, 95% CI: 0.238, 1.170, p=0.130).

DISCUSSION

This study presents population-based estimates for the risk of revision following total joint replacement of the hip and knee using methods from survival analysis. Cumulative incidence rates of revision were higher for men than for women and higher for hips than knees. Age, gender and body mass index were estimated to be significant predictors of time to revision in an adjusted model allowing for the competing risk of death. Severely obese patients undergoing total hip replacement were observed to have a higher risk of revision surgery during the first year following replacement, but the same effect was not observed for knee replacement.

The literature on obesity as a risk factor for hip and knee arthroplasty concentrates mainly on the risk for primary replacement rather than for revision procedures, and most use rate differences to estimate relative risk, rather than using time-to-event methods. Many published studies are small and do not have sufficient power to detect rare outcomes. Often these studies are locally based and the generalisability to population level is questionable. Mostly results are presented for categorised BMI, which is often dichotomised at 30 kg/m², and where results for the morbidly obese are reported, the sample size is small.

One of the largest studies examining primary replacement followed up a cohort of over 490,000 middle-aged women over an average of 2.9 years and found increased incidence of hip and knee replacement in obese subjects(18). Of the studies which consider the effect of obesity on outcomes after primary joint replacement, several focus mainly on events such as complications arising from surgery(19) or subsequent admission to an intensive care unit(20), rather than the time to revision surgery. Among studies of other non-revision outcomes, Andrew *et al*(21) looked at the change in Oxford Hip Score five years after THR and found no difference between non-obese, obese and morbidly obese patients, but in a smaller study(22) using Harris Hip Score (HHS) with the same length of follow-up, an increase in BMI was associated with a small but significant reduction in HHS.

An editorial on obesity and joint replacement in 2006(23) suggested that it is those with a BMI of greater than 40 units (rather than 30) who are at risk of worse outcomes, yet several subsequent studies have used a BMI cut-point of 30 kg/m². A recent Australian study of 2026 THR and 535 TKR patients found no difference in mid-term survival rates between the obese (BMI > 30 kg/m²) and non-obese(24). Another study from Switzerland used Cox regression to estimate the risk of revision in 2495 THRs using the same cut-point for BMI, estimating a non-significant adjusted hazard ratio for revision of 2.2 (95% CI: 0.9 to 5.3) for obese versus non-obese patients(19). However, a recent Canadian study of 3290 THRs did categorise BMI to include a morbidly obese group (BMI > 40 kg/m²) and although

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the authors found no difference in time to revision between BMI categories in an unadjusted analysis, there was a marginally significant difference for septic revisions(25).

Our results suggest that there may be a 1.5% to 2% rise in the risk of knee and hip revision respectively for each extra unit of BMI. However, there is some variation in risk across the entire range of observed BMI values. For hips, there appears to be very little difference in BMI-related risk between the normal weight and overweight categories. However, figure 1a shows that for hips there may be a revision rate of approximately 6% for the morbidly obese after 10 years, against a 3% rate for the normal and overweight. For knees, figure 1b shows a more even distribution across the BMI categories up to about 7 years after TKR, but with higher risk for the morbidly obese between 7 and 10 years after TKR.

Although recommendations(26, 27) to consider the use of the cumulative incidence function for analysing prosthesis survival are gaining acceptance(28), the use of competing risks regression to model associated risk factors is still not widely observed. The justification for using competing risks methods in our primary analysis is that hip and knee prostheses are mainly implanted in older patients for whom mortality is a substantial competing risk which may be several times greater than the risk of revision. What is perhaps surprising is that our results show little difference between the hazard and subhazard ratio estimates from the Cox and the competing risks regression models respectively, although the former has a cause-specific interpretation with no distinction between death and censoring whereas the latter directly models the cumulative incidence of revision.

Strengths and potential limitations of the study

The strengths of the study data more than make up for its limitations. GPRD data has individual date-stamped records of patient event data in primary and secondary care settings, including data on many potential confounders, including comorbidities, BMI, smoking and drinking. The GPRD practice network covers all of the United Kingdom, and approximately 5% of all practices are covered by the GPRD. The high degree of generalisability afforded by this very large sample enables population-level inferences to be made. Follow-up is long, with several hundred prostheses in the dataset having over 20 years of follow-up without being revised. The choice of the statistical methods used to allow for the competing risk of death adds a further degree of robustness to the study. The regression estimates of the hazard ratio for body mass index as a factor associated with revision benefit from a precision which is not usually achievable outside of national registers, especially for the group of morbidly obese patients within which event rates in the literature are low.

There are several limitations to this work. The revision rate estimates hip and knee at 5 years are close to, but slightly less than those reported by the National Joint Registry, but the GPRD data used in this study includes prostheses implanted from the late 1980s. Also our data does not have directly linked information on the indication for surgery, which would have been enabled a sub-analysis by reason for revision. Although certain indications for revision are more common than others depending on follow-up time (e.g. infection occurring early), any inferences about indication-specific risks before or after a given follow-up time would not have been reliable.

CONCLUSION

This study has presented estimates of rates and risk factors for revision surgery on hip and knee prostheses using one of the largest available population-based sets of joint replacement data outside of national arthroplasty registries. Our estimates suggest that

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body mass index is positively associated with the risk of hip and knee revision, but studies of register data linked with sources of demographic and clinical data are needed in order to distinguish between effects for specific indications for revision surgery.

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Author affiliations

[1]Faculty of Medicine, University of Southampton, Tremona Road, Southampton. SO16 6YD.

[2]Public Health Sciences and Medical Statistics, Faculty of Medicine, University of Southampton, Tremona Road, Southampton, SO16 6YD.

[3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD.

[4]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, SO16 6YB.

Collaborators The following people are members of the COAST Study group: Cyrus Cooper, Mark Mullee, James Raftery, Andrew Carr, Andrew Price, Kassim Javaid, David Beard, Douglas Altman, Nicholas Clarke, Jeremy Latham, Sion Glyn-Jones and David Barrett.

Contributors DJC, JM, AJ and NKA were involved in:
(1) substantial contributions to conception and design, analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

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Data sharing statement No additional data are available.

Table 1 Clinical and Demographic characteristics – all subjects undergoing Total Hip or Knee Replacement

	Total Hip Replacement (N=63,162)		**Total Knee Replacement** (N=54,276)	
	Female (N=39,292)	Male (N=23,870)	Female (N=31,682)	Male (N=22,594)
Age (mean, SD)	70.5 (11.1)	67.7 (11.0)	70.7 (9.6)	69.4 (9.4)
Gender (%)	62.2	37.8	58.3	41.6
BMI (mean, SD)	27.2 (5.1)	27.7 (4.3)	29.6(5.6)	28.8(4.4)
Missing BMI (%)	19.1	19.3	13.8	14.0
Revisions (N, %)	1000 (2.55)	811 (3.40)	572 (1.8)	614 (2.7)
Deaths pre-revision (N, %)	6615 (16.8)	4201 (17.6)	4110(13.0)	3349 (14.8)
Number of comorbid conditions (%):				
0	42.8%	48.1%	37.5%	43.7%
1	34.2%	31.0%	37.4%	35.8%
2+	23.0%	20.9%	25.2%	20.6%

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Table 2 Cumulative incidence rates for revision surgery at selected times following THR and TKR

	Hip				Knee			
	Female		Male		Female		Male	
Years since total joint replacement	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval	Cumulative incidence of revision (%)	95% Confidence Interval
1	0.6	(0.5, 0.6)	0.7	(0.6, 0.8)	0.3	(0.2, 0.4)	0.4	(0.3, 0.5)
3	1.2	(1.1, 1.3)	1.4	(1.3, 1.6)	1.1	(1.0, 1.2)	1.5	(1.4, 1.7)
5	1.8	(1.7, 2.0)	2.2	(2.0, 2.4)	1.6	(1.5, 1.8)	2.3	(2.1, 2.6)
10	3.4	(3.1, 3.6)	4.6	(4.3, 5.0)	2.8	(2.5, 3.1)	4.5	(4.1, 4.9)
15	6.0	(5.5, 6.6)	8.3	(7.6, 9.1)	4.4	(3.9, 5.0)	7.1	(6.2, 8.1)

Table 3a Estimated subhazard of revision for Total Hip Replacement – Competing risks analysis

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m²) (per additional unit)	1.030	(1.020, 1.041)	<0.001	1.020	(1.009, 1.032)	<0.001
Gender						
Female (reference)	1.00			1.00		<0.001
Male	1.35	(1.23, 1.48)	<0.001	1.23	(1.10, 1.38)	
Age (years at THR) (per additional year)	0.970	(0.967, 0.973)	<0.001	0.971	(0.966, 0.975)	<0.001
BMI[a] (kg/m²) (per additional unit)	1.030	(1.020, 1.041)	<0.001	1.020	(1.009, 1.032)	<0.001

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

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Table 3b Estimated subhazard of revision for Total Knee Replacement – Competing risks analysis

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[b] (kg/m²) (per additional unit)	1.026	(1.013, 1.038)	<0.001	1.015	(1.002, 1.028)	0.023
Gender						
Female (reference)	1.00			1.00		
Male	1.54	(1.37, 1.72)	<0.001	1.51	(1.32, 1.73)	<0.001
Age (years at THR) (per additional year)	0.957	(0.952, 0.961)	<0.001	0.957	(0.951, 0.962)	<0.001
~~**BMI**[b] (kg/m²) (per additional unit)~~	~~1.026~~	~~(1.013, 1.038)~~	~~<0.001~~	~~1.015~~	~~(1.002, 1.028)~~	~~0.023~~

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Table 4a Estimated hazard of revision for THR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			Adjusted[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m[2]) (per additional unit)	1.029	(1.017, 1.040)	<0.001	1.019	(1.008, 1.031)	0.001
Gender						
Female (reference)	1.00			1.00		
Male	1.36	(1.24, 1.29)	<0.001	1.26	(1.13, 1.41)	<0.001
Age (years at THR) (per additional year)	0.978	(0.974, 0.983)	<0.001	0.977	(0.972, 0.982)	<0.001
~~**BMI**[a] (kg/m[2]) (per additional unit)~~	~~1.029~~	~~(1.017, 1.040)~~	~~<0.001~~	~~1.019~~	~~(1.008, 1.031)~~	~~0.001~~

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 86.1% of patients

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Table 4b Estimated hazard of revision for TKR– Univariable and adjusted Cox regression analysis with death as a censoring event

	Univariable			**Adjusted**[a]		
	Hazard ratio	95% Confidence Interval	p-value	Hazard ratio	95% Confidence Interval	p-value
BMI[a] (kg/m[2]) (per additional unit)	1.024	(1.012, 1.037)	<0.001	1.015	(1.003, 1.028)	0.019
Gender						
Female (reference)	1.00			1.00		<0.001
Male	1.58	(1.41, 1.77)	<0.001	1.55	(1.36, 1.77)	
Age (years at THR) (per additional year)	0.962	(0.956, 0.967)	<0.001	0.961	(0.955, 0.968)	<0.001
BMI[a] (kg/m[2]) (per additional unit)	1.024	(1.012, 1.037)	<0.001	1.015	(1.003, 1.028)	0.019

[a]Adjusted for smoking (Yes/No/Ex), drinking (Yes/No/Ex), number of comorbid conditions

[b]BMI available in 80.9% of patients

Figure 1a Cumulative incidence estimate for revision of THR by body mass index

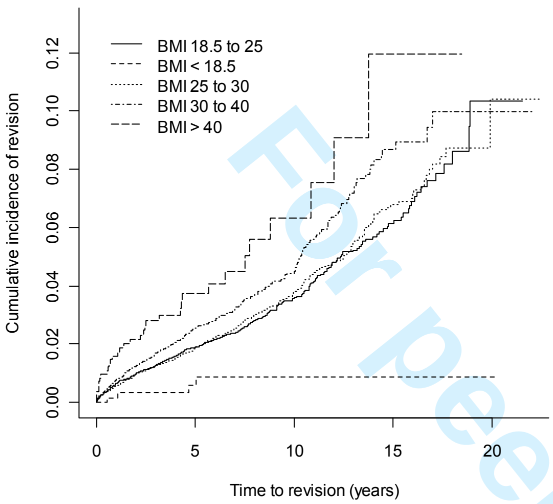

Figure 1b Cumulative incidence estimate for revision of TKR by body mass index

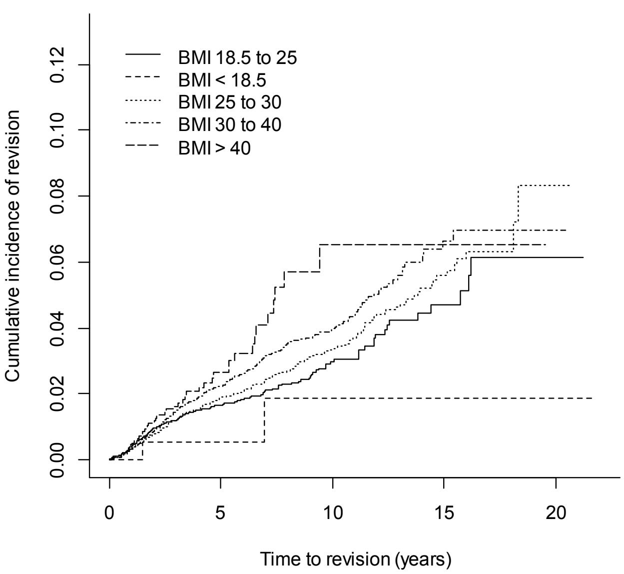

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Figure 2a Cumulative incidence estimate for revision of THR by age

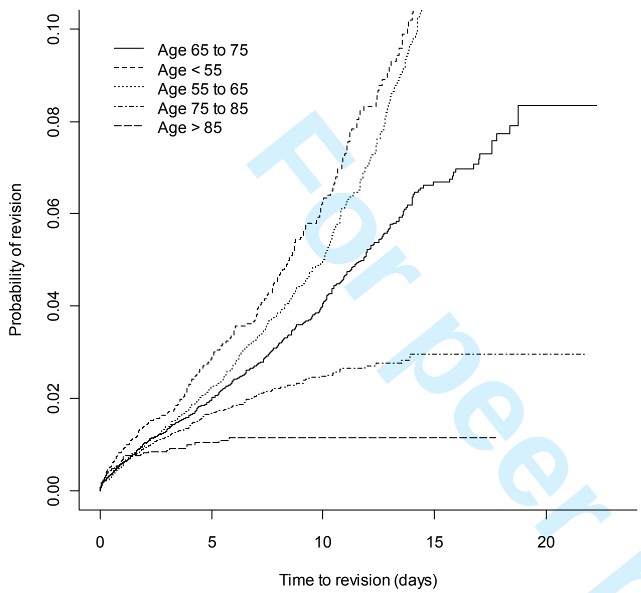
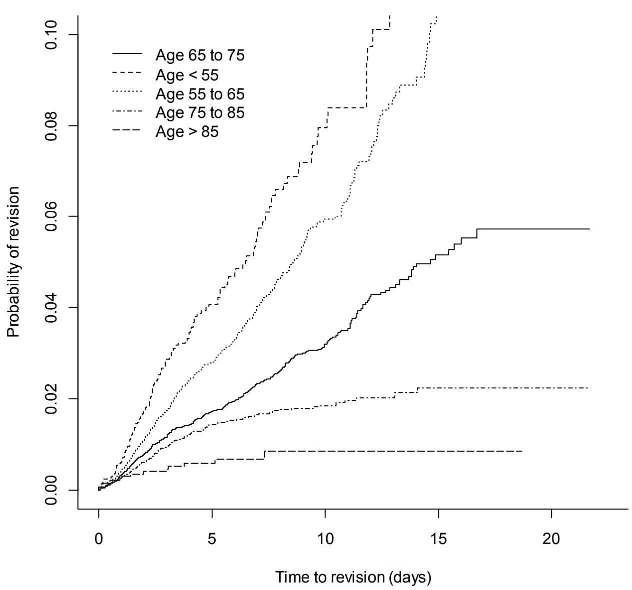


Figure 2b Cumulative incidence estimate for revision of TKR by age



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Population-based case cohort design *(*mentioned in Abstract/Method)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Competing risks survival (mentioned in Abstract/Method)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Age/gender available in National Joint Registry, but BMI has missing data. GPRD has good level of completeness for BMI.
Objectives	3	State specific objectives, including any prespecified hypotheses To provide population-based estimates for the effects of BMI on time to revision, with long follow-up (mentioned in Introduction).
Methods		
Study design	4	Present key elements of study design early in the paper Method of Fine and Gray referred to (top of Analysis subsection in Methods section)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Fully described in Participants subsubsection in Methods section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *"all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1991 until August 2011"*, quoted in the Participants subsubsection in Methods section.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable All defined in the Analysis subsection in Methods section: Outcome: time to first incidence of revision surgery, predictors: BMI, age, gender, potential confounders: smoking status, alcohol consumption, number of comorbid conditions.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group In the Analysis subsection in Methods section. Single group comprising those undergoing total replacement of the hip/knee (no controls).
Bias	9	Describe any efforts to address potential sources of bias In the Analysis subsection in Methods section. Comorbid conditions are a possible source of bias, hence the adjustment.
Study size	10	Explain how the study size was arrived at Population-based study. The GPRD is sized to enable precise estimates for most geographic/demographic subgroups.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why BMI was grouped according to WHO guidelines.

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done (in Analysis subsection in Methods section).
		(*b*) Describe any methods used to examine subgroups and interactions Two-way interactions examined (described in Analysis subsection in Methods section)
		(*c*) Explain how missing data were addressed Presence of BMI (in table 1) was sufficiently complete (>80% knees; >85% hips) and age and gender were 100% complete.
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable in such a dataset (most patients remained registered with the same GP in the GPRD, those leaving are not traceable).
		(*e*) Describe any sensitivity analyses Cox regression used as a sensitivity vs. Competing Risks Regression (described in Analysis subsection in Methods section).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Numbers given in table 1.
		(b) Give reasons for non-participation at each stage Not applicable (population-based data)
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Characteristics given in table 1.
		(b) Indicate number of participants with missing data for each variable of interest Given for BMI (the only variable of interest with missingness)
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time Number of revisions reported in table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Provided in tables 2, 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized Done (Results section; subsection entitled Survival Analysis)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not appropriate for this data, although we have provided estimates of numbers needed to "treat" (NNT).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done (Piecewise analysis and Cox regression – both documented in Results section; subsection entitled Survival Analysis)
Discussion		
Key results	18	Summarise key results with reference to study objectives Described in first few paragraphs of discussion.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

		Limitations covered in penultimate paragraph of discussion (e.g. lack of reliable indication data, long follow-up but includes older prostheses).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Covered in the middle part of the discussion section.
Generalisability	21	Discuss the generalisability (external validity) of the study results Population-based study so results are generalisable to the (gender-specific) UK adult population as a whole. Stated in 'Strengths and Limitations' subsection of Discussion section.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based NIHR Programme Grant for Applied Research grant number given in relevant section immediately following the discussion.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.